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Multimodality imaging for myocardial injury in acute myocardial infarction and the assessment of valvular heart disease

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General introduction and outline of the thesis

GENERAL INTRODUCTION

The outcome of patients with ST-segment elevation myocardial infarction (STEMI) has significantly improved over the last decades.[1,2] Timely reperfusion with primary percutaneous coronary intervention (PCI) and implementation of evidence-based and guideline-recommended treatments have contributed significantly to these improved outcomes.[3,4] However, STEMI survivors are still at high risk of recurrent cardiovascular events such as congestive heart failure, arrhythmia, and sudden death.[5,6] Thus, the search continues for novel effective therapies that can be administered as an adjunct to primary PCI in STEMI to reduce myocardial infarct size and prevent heart failure.[7,8] In order to demonstrate a clear clinical benefit of any such intervention advanced cardiac imaging plays an important role. Although electrocardiogram, echocardiography, single photon emission computed tomography and cardiac biomarker release have been widely used, cardiovascular magnetic resonance (CMR) is currently the recommended technique for the assessment of myocardial injury in STEMI trials.[8,9] CMR is the gold standard to assess left ventricular ejection fraction (LVEF), the widely implemented functional parameter, and infarct size, the structural surrogate of myocardial infarction.[10] Both parameters have been associated with long-term mortality and morbidity after STEMI.[11,12] However, CMR also allows for the assessment of myocardial edema, microvascular damage and left ventricular (LV) strain, which can serve as powerful complementary tools to evaluate the benefits of cardioprotective therapies (Figure 1).

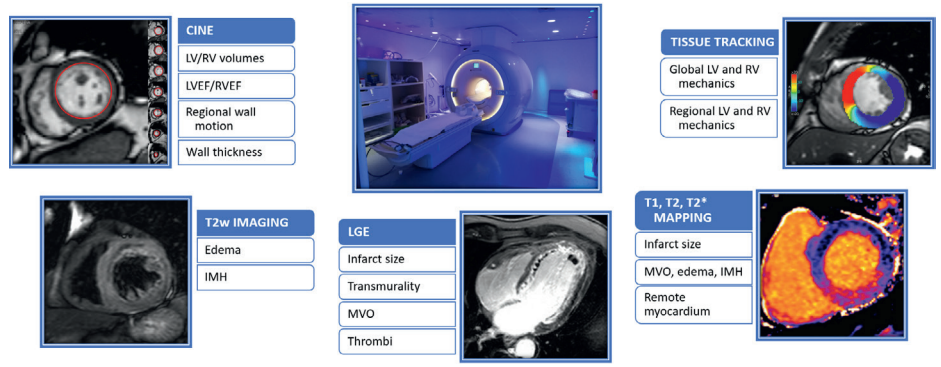

Figure 1: Cardiovascular magnetic resonance after acute myocardial infarction. Within a single scan, the assessment of left and right ventricular volumes and function, myocardial edema, infarct extent and transmurality, and microvascular damage can be performed. IMH, intramyocardial hemorrhage; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; MVO, microvascular obstruction; RV, right ventricular; RVEF, right ventricular ejection fraction; T2w, T2-weighted.

Multimodality cardiac imaging plays a central role in management of patients with valvular heart disease (VHD). Whenever VHD and heart failure coexist, advanced imaging may help answering the dilemma whether the LV dysfunction is due the disease of the valve or the ventricle.[13,14] In patients with transcatheter aortic valve replacement (TAVR) multiple imaging modalities define procedural planning, periprocedural guidance and long-term follow-up.[15,16] Furthermore, novel biomarkers of myocardial injury, like focal replacement and diffuse interstitial myocardial fibrosis with CMR, hold promise to redefine the optimal timing for intervention in asymptomatic patients with severe VHD.[17]

Cardiovascular magnetic resonance-derived left ventricular strain after acute myocardial infarction

Acute myocardial infarction results in myocardial cell necrosis and changes in extracellular collagen matrix that portend adverse consequences on LV structure and function.[18] While early intravenous beta-blocker administration offers physiological rationale for lowering the myocardial infarction burden,[19] their routine use has been disputed over the last decades due to conflicting data on patients outcome.[20] The Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial was the first randomized control clinical trial in the modern era of primary PCI, that showed a clear clinical benefit of early administration of intravenous beta blockade in STEMI patients.[21,22] Early intravenous metoprolol resulted in a significant reduction of LV end-systolic volumes, an increase in LVEF and a smaller infarct size, assessed with late gadolinium enhancement (LGE), 1 week after anterior STEMI, as evaluated with CMR imaging.[21] In addition, early metoprolol administration was associated with an improved LVEF after 6 months.[22]

While LVEF and infarct size are the cornerstones to evaluate myocardial injury after acute myocardial infarction, LV strain assessment can provide additional important information. It detects subtle systolic dysfunction in patients with preserved LVEF and allows excellent intra- and inter-observer reproducibility.[23,24] Moreover, LV strain with speckle tracking echocardiography has shown incremental prognostic value to predict adverse LV remodeling and outcome after STEMI.[25,26] On the other hand, LV strain with CMR has been much less extensively evaluated, mainly due to the complex acquisition and postprocessing techniques. Until recently, LV strain with CMR could only be investigated with tissue tracking technologies, such as myocardial tagging, strain encoded (SENC) imaging, displacement encoding with stimulated echoes (DENSE) imaging, which rely on specialized pulse sequences and additional scanning

time.[27] However, recent development of feature-tracking CMR, a post-processing software platform that allows multidirectional LV strain assessment from routinely acquired functional cine images (in a similar fashion to speckle-tracking echocardiography), has opened a gateway to wider implementation of LV strain assessment with CMR in the research and clinical practice.[28,29] Time course of global LV longitudinal (GLS) and circumferential (GCS) strain after acute myocardial infarction has not yet been evaluated with feature-tracking CMR. In addition, the impact of early intravenous metoprolol on global LV myocardial strain in the acute and chronic stage of STEMI remain to be elucidated.

The tissue healing process after reperfused myocardial infarction is complex and affects the infarcted area as well as the distant myocardium.[30,31] Several studies have described the evolution of regional LV strain with CMR after myocardial infarction, mostly showing gradual improvement of LV strain in the infarct zone and no significant changes in the remote zone.[32-36] However, none of them employed the novel feature-tracking algorithm to investigate regional LV strain. Furthermore, it remains to be elucidated whether the cardioprotective effects of early intravenous metoprolol are confined to the infarct zone strain, remote zone strain or both. There is as well conflicting evidence on the impact of microvascular obstruction (MVO) and intramyocardial hemorrhage (IMH), both surrogates of microvascular damage in acute myocardial infarction, on regional strain recovery.[34-36] Finally, the effect of adverse LV remodeling (commonly defined as ≥20% increase in LV end-diastolic volume) on the infarct and remote zone myocardial strain has not yet been evaluated.

While the results of the METOCARD-CNIC clinical trial have shown a clear clinical benefit among patients receiving early intravenous metoprolol in terms of smaller LV infarct size[21] and more preserved long-term LV systolic function[22] this has not been fully translated into improved patient prognosis. Namely, early intravenous metoprolol administration was associated with a nonsignificant trend towards reduced occurrence of pre-specified MACE (10.8% in the metoprolol group versus 18.3% in the control group; P=0.065) at a median follow-up of 2 years.[22] However, the prognostic value of early intravenous metoprolol has not yet been explored with longer follow-up data. In addition, the prognostic value of global LV strain with feature tracking CMR over traditional markers of myocardial injury, such as LVEF and infarct size with LGE should be evaluated, especially in the view of the recent studies showing conflicting results.[37-40] Finally, it remains to be elucidated whether the association between global LV strain and prognosis is modulated by the early intravenous metoprolol treatment.

Multimodality cardiac imaging in valvular heart disease

VHD and heart failure are major health issues that are steadily increasing in prevalence in Western populations.[41-44] VHD and heart failure frequently co-exist, which can complicate accurate diagnosis of the severity of valve stenosis or regurgitation and affect therapy.[45,46] Cardiac imaging plays a central role in determining the mechanism and the severity of VHD as well as the degree of accompanying LV remodeling and systolic dysfunction. Furthermore, the decision upon the optimal treatment strategy (e.g., surgical valve repair versus replacement, feasibility of percutaneous valve interventions) rely heavily on accurate and detailed cardiac imaging.[41,42] Echocardiography is the primary imaging modality and may be complemented by cardiac computed tomography (CT) and CMR when additional anatomical or functional information is needed.

Over the last decades, TAVR has emerged as an effective alternative to surgical aortic valve replacement for patients with symptomatic severe aortic stenosis.[41,42] Patient selection, accurate sizing of the prosthesis, choice of the procedural approach requires the use of several imaging modalities to optimize the results and minimize complications such as paravalvular regurgitation, aortic annulus rupture, pacemaker implantation or vascular injury.[15,47] Multidetector row computed tomography (MDCT) has become the key imaging modality for pre-procedural evaluation of TAVR candidates in most centers due to its low invasiveness and comprehensive evaluation. Procedural guidance is mainly performed with fluoroscopy assistance, however, in high-risk situations transthoracic echocardiography or transesophageal echocardiography (TEE) can be employed. Prosthesis durability, indices of valve stenosis and regurgitation, thrombosis, infective endocarditis and LV function and remodeling are the key imaging parameters during the follow-up of TAVR patients.

Selection of appropriate TAVR prosthesis size relies on accurate measurement of the aortic annulus, which is a virtual ring at the hinge points of the aortic valve leaflets and as such difficult to characterize with 2-dimensional imaging techniques.[48] Although MDCT is currently considered the reference standard to measure the aortic valve annulus, it requires the use of nephrotoxic contrast and data acquisition during the systolic phase may lead to motion artifacts that reduce the accuracy of the aortic annulus measurements. In contrast, 3-dimensional (3D) TEE permits the acquisition of 3D data along the entire cardiac cycle with adequate temporal and spatial resolution, allowing for accurate measurements of the aortic annulus.[49,50] Recently, automated software for post-processing of 3D TEE datasets have been developed. However, a head-to-head comparison between MDCT and dedicated automated 3D TEE software for aortic annulus assessment and TAVR prosthesis size selection has not yet been performed. Furthermore, the effect of the aortic valve calcification burden on the accuracy of the 3D TEE measurements has not yet been studied.

The decision to operate in patients with severe VHD is frequently complex and relies on an individual risk-benefit analysis. Current guidelines recommend to intervene in patients with symptomatic severe VHD and in asymptomatic patients with reduced LVEF, LV dilatation, pulmonary hypertension, right ventricular dilatation and dysfunction and presence of atrial fibrillation.[41,42] However, most of these adverse consequences of severe VHD are observed in advanced stages of the disease and are partially irreversible after intervention, leading to suboptimal long-term clinical outcomes.[51] Therefore, additional markers that identify early structural and functional consequences of severe VHD would help to redefine the optimal timing for intervention. CMR imaging with T1 mapping and LGE assessment permit myocardial tissue characterization and provide measures of focal replacement and diffuse myocardial fibrosis, whereas CMR tagging and feature-tracking CMR allow for the assessment of myocardial deformation (strain), a functional parameter that indirectly reflects myocardial fibrosis. Accumulating evidence on the deleterious impact of LV myocardial fibrosis on clinical outcomes after surgical treatment of left-sided VHD has raised interest on tissue characterization with CMR techniques.[52-55]

Recent investigations demonstrated an association between mitral valve prolapse (MVP) and malignant ventricular arrhythmias.[56-58] Various imaging parameters have been proposed to predict the risk for developing malignant ventricular arrythmias and sudden cardiac death in patients with MVP, among which fibrosis of the papillary muscles and of the inferolateral LV wall has gained prominence.[59-62] However, it remains to be elucidated whether MVP also associates with diffuse myocardial fibrosis, detected with novel CMR techniques such as extracellular volume (ECV). Moreover, the interplay between patient characteristics, mitral regurgitation grade and markers of LV fibrosis needs to be explored in order to translate this information into clinical practice.

OUTLINE OF THE THESIS

The objective of this thesis was twofold: i) to evaluate myocardial injury and cardioprotective effects of early intravenous metoprolol after STEMI with feature-tracking CMR, and ii) to explore the role of multimodality cardiac imaging in patients with VHD.

In **Part I** the role of LV strain with feature-tracking CMR among patients included in the METOCARD-CNIC randomized clinical trial is investigated. **Chapter 2** focuses on the changes in GLS and GCS from the first week to 6 months after STEMI and explores the impact of early intravenous metoprolol on global LV strain. In **Chapter 3** the effects of early intravenous metoprolol treatment, MVO, IMH and adverse LV remodeling on the evolution of infarct and remote zone circumferential strain over 6 months after STEMI are evaluated. In **Chapter 4** long-term 5-year follow-up results of the patients included in the METOCARD-CNIC trial are presented. The prognostic value of early intravenous metoprolol, GCS, GLS and the association between global LV strain and early intravenous metoprolol treatment on patient prognosis are analyzed.

Part II provides a perspective on the use of multimodality cardiac imaging in VHD. In **Chapter 5**, the role of echocardiography, cardiac CT and CMR in patients with VHD and heart failure is discussed. **Chapter 6** provides an overview of the advantages and limitations of different cardiac imaging techniques in the evaluation of patients undergoing TAVR. In **Chapter 7**, novel automated 3D TEE software is compared to the gold-standard MDCT for the aortic annulus sizing and prosthesis selection in TAVR patients. In addition, the influence of the quantity of aortic valve calcium on the accuracy of the 3D TEE algorithm and the selection of TAVR prosthesis size is explored. **Chapter 8** summarizes the current status of CMR techniques to assess myocardial fibrosis and appraises the current evidence on the use of these techniques for the risk stratification of patients with severe VHD. In **Chapter 9** the role of myocardial fibrosis is further explored in patients with MVP.

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